

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
3 March 2005 (03.03.2005)

PCT

(10) International Publication Number
WO 2005/019152 A3

(51) International Patent Classification⁷: C07C 67/10, 69/734 PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number: PCT/IN2004/000156

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date: 4 June 2004 (04.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 586/MUM/2003 6 June 2003 (06.06.2003) IN

(71) Applicant (for all designated States except US): CADILA HEALTHCARE LIMITED [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BAROT, Vijay, Kumar, Gajubhai [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN). KOTHARI, Himanshu, Madhusudanbhai [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN). LOHRAY, Braj, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN). LOHRAY, Vidya, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN).

(74) Agents: SUBRAMANAM, Hariharan et al.; Subramaniam, Nataraj & Associates, E-556, Greater Kailash-II, New Delhi 110 048, Maharashtra (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report: 11 August 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/019152 A3

(54) Title: PROCESS FOR PREPARING 3-ARYL-2-HYDROXY PROPAANOIC ACID DERIVATIVES WITHOUT RESOLUTION

(57) Abstract: The present invention discloses an improved process for the preparation of S (-) & R (+) 3-aryl-2-hydroxy propanoic acid derivatives without any resolution involved.

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HSM-MC-014	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/IN2004/000156	International filing date (day/month/year) 04.06.2004	Priority date (day/month/year) 06.06.2003
International Patent Classification (IPC) or national classification and IPC C07C67/10, C07C69/734		
Applicant CADILA HEALTHCARE LIMITED		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau)</i> a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only)</i> a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 03.01.2005	Date of completion of this report 10.10.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Sen, A Telephone No. +49 89 2399- 	

INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITYInternational application No.
PCT/IN2004/000156

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-21 as originally filed

Claims, Numbers

1-27 as originally filed

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. The amendments have resulted in the cancellation of:
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):
4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IN2004/000156

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	26-27
	No: Claims	1-25
Inventive step (IS)	Yes: Claims	
	No: Claims	1-27
Industrial applicability (IA)	Yes: Claims	1-27
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/IN2004/000156

D1: WO 02/24625 A (DR. REDDY'S RESEARCH FOUNDATION; POTLAPALLY, RAJENDER, KUMAR; SIRIPRAG) 28 March 2002 (2002-03-28)
D2: WO 03/027084 A (DR. REDDY'S LABORATORIES LTD; POTLAPALLY, RAJENDER, KUMAR; SIRIPRAGADA) 3 April 2003 (2003-04-03)
D3: US-B1-6 258 850 (ANDERSSON KJELL) 10 July 2001 (2001-07-10)

SECTION V:

Novelty - The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the claims 1-25 is not new in the sense of Article 33(2) PCT in view of the prior art documents D1 - D2.

Accordingly D1 describes a process for the preparation of the S(-) isomer of 3-aryl-2-alkoxy propanoic acid which comprises the selective benzylation of L-tyrosine (see D1: compound (14) to compound (15)) to yield (S)-2-amino-3-(4-benzyloxyphenyl)-propanoic acid; diazotisation using a diazotising agent to produce (S)-2-hydroxy-3-(4-benzyloxyphenyl)propanoic acid (see D1, compound (8a)); simultaneous etherification and esterification (see D1, compound (9)); and deprotection of the protecting group to obtain a compound corresponding to compound (1a) according to the present application (see D1: compound (1); see page 8, lines 12-16; page 14, step (vii); and see also page 3, Scheme 4; page 6, Scheme 6, "(15) → (8a)"; page 8, lines 12-16; page 9, lines 1-24; claims; see D2: page 4, Scheme 4, "(22) → (11a)"; page 12, Scheme 6, page 26, Example 8, steps I and ii).

With regard to claims 26 and 27, the difference between D1/D2 and the subject-matter of claims 26 and 27 is that the process according to 26 and 27 relates to the preparation of the R(+) isomer of 3-aryl-2-alkoxy propanoic acid. Accordingly, instead of starting with L-tyrosine (see claims 1-25), the process according to claims 26 and 27 uses D-tyrosine as starting material, all the following steps being the same.

At the light however of the detailed description provided in the prior art of the reaction sequence as described in the application, starting from the selective benzylation, diazotisation, etherification and esterification to the deprotection to obtain the target compound, also optically and chemically pure and without resolution, an inventive step cannot be recognized.

Accordingly, the subject-matter of the application does not meet the requirements of Article

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/IN2004/000156

33() PCT, because the subject-matter of the claims does not involve an inventive step in the sense of Article 33(3) PCT.